U.S. Pharmacopeia
The Standard of Quality℠

99N-1174

MEETING OF THE FOOD AND DRUG ADMINISTRATION
June 8, 1999

Overall Strategy for Achieving Effective Regulation of Dietary Supplements Under The Dietary Supplement Health and Education Act

Remarks by the United States Pharmacopeia
Joseph G. Valentino, Sr. Vice-President
and General Counsel

12601 Twinbrook Parkway
Rockville, MD 20852

301-881-0666
www.usp.org

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On behalf of the United States Pharmacopeia (USP), I submit these comments in response to the Food and Drug Administration's (FDA) request for information on an overall strategy for achieving effective regulation of dietary supplements. USP, established in 1820, is a not-for-profit, voluntary organization that promotes the public health by establishing and disseminating officially recognized standards of quality for medicines and other health care technologies.

Based on concerns about the identity, safety, quality, and purity of dietary supplements, USP has set standards for these products and has provided a chapter on manufacturing practices for nutritional supplements. USP encourages the Food and Drug Administration to recognize *United States Pharmacopeia-National Formulary (USP-NF)* monographs for dietary supplements, to work with USP to develop standards for botanical dietary supplement products, and to encourage the use of these standards by industry. USP also encourages the agency to enforce *USP-NF* standards to ensure the purity, potency, quality, and most important, the safety of dietary supplements. In addition, USP recommends that FDA carefully review product labeling to ensure that it accurately states compliance with *USP-NF* standards and that it does not contain statements that are false or meaningless or designed to mislead the consumer as to the quality of the product; such as: "standardized," "meet laboratory standards," and "meet USP dissolution standards." The first two statements do not provide useful information to consumers; the third statement may be misleading if the product meets *USP* dissolution standards but fails to meet other *USP* quality standards.

USP intends to establish standards for the major nonbotanical dietary supplements on the U.S. market, including glucosamine sulfate, chrondroitin sulfate, coenzyme Q-10, and others to provide American consumers with the same level of protection that is being afforded through *USP* botanical-based dietary supplements standards. FDA is encouraged to work with USP to develop standards for these products also.

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As requested by FDA, USP has set forth its responses to each of the agency's question as described in the *Federal Register* Notice, (64 Fed. Reg. 25889, May 13, 1999).

1. *In addition to ensuring consumer access to safe dietary supplements that are truthfully and not misleadingly labeled, are there other objectives that an overall dietary supplement strategy should include?*

   FDA's overall strategy should ensure the identity, safety, purity, and quality of dietary supplement products. This strategy also should ensure consistency and uniformity of product strength and identity so that consumers can make an informed selection among dietary supplements. To implement this strategy, FDA should require that quality materials are used to manufacture dietary supplements by providing guidance on the analytical methods and procedures used in the industry. FDA should also standardize product labeling to identify the active ingredient(s) and strength based on these standards.

2. *Are the criteria for prioritizing the tasks within the supplement strategy appropriate? Which specific tasks should FDA undertake first?*

   USP agrees with the agency that the most important priority is to ensure consumer safety. To do so, USP recommends that FDA identify those botanicals and non-botanical based dietary supplements used by a majority of consumers in the United States and implement standards for these products. For example, with respect to botanicals, USP has focused its standard-setting efforts on approximately 24 botanicals, which account for 90% of sales to consumers. Standards are being provided for plant part(s), primary extracts, and the most common dosage forms. USP also encourages the agency to settle unresolved regulatory issues, particularly with respect to the standardization of quality of dietary supplements.

3. *What factors should FDA consider in determining how best to implement a task?*

   In the FDA 2000 strategic plan, the theme of FDA working in partnership occurs repeatedly. USP stands ready to work in partnership with FDA to provide standards and analytical methods that will ensure quality dietary supplements.

4. *What tasks should be included under the various dietary supplement program elements in the CFSAN 1999 Program Priorities document?*

   USP recommends that FDA require compliance with *USP-NF* standards that would ensure safe dietary supplements of high quality. In addition, FDA should provide final regulations on the good manufacturing practices for dietary supplement manufacturers and provide regulations on enforcement of standards and GMPs. USP recommends that FDA incorporate into GMPs the USP chapter on Nutritional Supplements. USP also encourages the FDA to work with the USP Practitioner and Product Experience Division to obtain reports on issues of product quality of dietary supplements. With respect to health claims, FDA's effort should focus on ensuring that such claims have adequate support, especially for dietary supplements that have been reported to cause adverse effects, such as ephedra, comfrey, chapparal.

5. *Are there current safety, labeling, or other marketplace issues that FDA should address quickly through enforcement actions to ensure, for example, that consumers have confidence that the products on the market are safe and truthfully and not misleadingly labeled?*

   FDA should identify dietary supplements that contain ingredients that are unsafe and remove these products from the market.

   FDA should take action on companies that erroneously claim or imply compliance with *USP* methods or provide a false sense of security that the product meets standards. For example, products that claim "standardized,"or "meet laboratory standards," or "meet USP dissolution standards" should not be permitted because these claims imply compliance with products that meet *USP-NF* standards. The first two statements do not provide useful information to consumers; the third statement may be misleading if the product meets *USP* dissolution standards, but fails to meet other *USP* quality standards.

   FDA should work with FTC to review evidence behind labeling claims, some of which are vague or nonspecific, to determine whether there is substantiation for the claim. Substantiation of labeling claims is necessary to ensure that consumer expectations of a product are met and to build consumer confidence in the quality of dietary supplement products.

6. *Toward what type or area of research on dietary supplements should FDA allocate its research resources?*

   FDA need not focus its limited resources on standard developments, since USP already is addressing this area. Instead, FDA should focus its research on standards enforcement, standardization in product ingredient and labeling, and substantiation of labeling claims.

7. *Given FDA's limited resources, what mechanisms are available, or should be developed to leverage FDA's resources to meet effectively the objective of the strategy?*

   FDA should publish monographs for dietary supplements modeled after those for OTC products published in the *Code of Federal Regulations*, incorporating recognition of USP standards for dietary ingredients. Monograph development should focus on botanicals that account for most of consumer sales and those that have the highest safety concerns. Last, FDA must ensure that industry complies with these standards.

Thank you for this opportunity to comment on FDA's strategy for regulation of dietary supplements. If you have questions or require more information, please do not hesitate to contact me.

Botanicals: Standards and Information

Monographs for botanical standards

- *USP*: (1) FDA-approved or USP-accepted use; and
  (2) No safety problems.
- *NF*: (1) No FDA or USP accepted use;
  (2) Used for a material time and extent; and
  (3) Absence of significant safety risk.

USP Information and Standards Botanical Monograph Development
Status Report

BOTANICAL PRODUCT	INFORMATION DEVELOPMENT STATUS	STANDARDS DEVELOPMENT STATUS
Angelica		Development work on hold
Comfrey	Final monograph (negative), December 1997 *USP DI Update*	None
Cranberry Cranberry Liquid Preparation		Supplement 10 (effective official date May 15 1999)
Echinacea purpurea Leaf with Flower		Draft to appear under Preveiws PF 25 (3) 1999
Ephedra or Ma Juang		Monograph being developed–no *PF* publication date at this time
Feverfew Feverfew Powdered Feverfew	Final monograph, February 1998 *USP DI Update*	Official in Supplement 9 (November 1998)
Garlic Garlic Powdered Garlic	Monograph being developed	Monographs official in the *Eighth Supplement* (May 1998)
Ginger Ginger Powdered Ginger	Final monograph, December 1997 *USP DI Update*	Monographs official in the *Seventh Supplement* (Nov. 1997)
Ginkgo Ginkgo Powdered Ginkgo Extract	Monograph being developed	Official in Supplement 9 (November 1998) Previews in PF 25 (3) 1999
Oriental Ginseng Oriental Ginseng Powdered Oriental Ginseng Powdered Oriental Ginseng Extract **American Ginseng** **Siberian Ginseng**	Monograph being developed	Official in Supplement 9 (Novemebr 1998)) Draft monograph under review Draft under preparation Monograph on hold
Golden Seal Root		Development pending

BOTANICAL PRODUCT	INFORMATION DEVELOPMENT STATUS	STANDARDS DEVELOPMENT STATUS
Hawthorn Hawthorn Leaf with Flower Powdered Hawthorn Leaf with Flower	Monograph being developed	Monographs appeared under *Pharmacopeial Previews* in *PF* 24(1) [Jan.–Feb. 1998]; and *In-Process Revision* in *PF* 24(5) [Sept.–Oct. 1998] Monographs under further evaluation by the Advisory Panles
Kava Kava		Development work on hold
Licorice		Development work on hold
Chamomile	Monograph being developed	Official in Supplement 9 (November 1998)
Milk Thistle Milk Thistle Powdered Milk Thistle	Monograph being developed	Official in Supplement 10 (effective official date May 15 1999)
Nettle Root		Development work on hold
Saw Palmetto Saw Palmetto Powdered Saw Palmetto	Monograph being developed	Official in Supplement 9 (November 1998) Official in Supplement 10 (effective official date May 15 1999)
St. John's Wort (Hypericum) St. John's Wort Powdered St. John's Wort Powdered St. John's Wort Extract	Final monograph, May 1998 *USP DI Update*	Official in Supplement 9 (November 1998) Draft to appear as Previews in PF 25(2) 1999.

BOTANICAL PRODUCT	INFORMATION DEVELOPMENT STATUS	STANDARDS DEVELOPMENT STATUS
Valerian Valerian Powdered Valerian Powdered Valerian Extract **General Test Chapter Extracts <565>**	Final monograph, December 1997 *USP DI Update*	Monographs official in the *Eighth Supplement* (May 1998) Appears under *Pharmacopeial Previews* in *PF* 24(5) [Sept.–Oct. 1998]. Forwarded to In-process-revision in PF 25 (3) 1999. Appears under *Pharmacopeial Previews* in *PF* 24(5) [Sept.–Oct. 1998]. Forwarded to In-process - revision PF 25 (2)1999

Garlic

» Garlic consists of the fresh or dried compound bulbs of *Allium sativum* Linné (Fam. Liliaceae).

Packaging and storage—Store in well-closed containers in a cool, dry place, protected from light.

Labeling—The label states the Latin binomial name and, following the official name, the part of the plant contained in the article.

USP Reference standards ⟨11⟩—*USP Alliin RS. USP L-Methionine RS.*

Botanic characteristics—

Macroscopic—Subglobular compound bulbs, 3 to 5 cm in width, consisting of 8 to 20 cloves, the whole surrounded by 2 to 5 layers of white scale leaves attached to a flattened, circular base; cloves ovoid and 3- to 4-sided, summit acute, narrowed into a threadlike portion of fiber base, truncate, each clove covered with a white scale leaf and a pinkish white epidermis, easily separated from the solid portion, consisting of two flaky scale leaves and two yellowish green conduplicate foliage leaves.

Microscopic—The protective leaf contains an epidermis enclosing a mesophyll free from chlorophyll. The outer epidermis consists of lignified sclereid cells of thick, pitted walls, elongated, covered with thin cuticle, long fibers up to 500 μm in length and 30 μm in width.

The cortical cells are thick-walled, nonlignified, tending to collapse on maturity, isodiametric, and contain purple pigments. The vascular bundles consist of lignified spiral and annular vessels. The storage leaves show an outer epidermis of thin, delicate cells of variable shape, arranged in somewhat irregular rows, 60 μm in length and 30 μm in width. Stomata are present on the outer epidermis only at the extreme tip near the base of the foliage leaves.

The mesophyll consists of swollen storage parenchyma cells filled with fine granular reserve material; scattered in the cortex are about 20 laticiferous tubes, 500 to 1000 μm in length. Two series of vascular bundles consisting of narrow lignified spiral and annular vessels are arranged in the mesophyll.

Identification—

A: Cut a freeze-dried garlic bulb into small pieces, transfer about 1 g of the cut pieces to an extractor, and extract with two 20-mL portions of a mixture of methanol and water (1 : 1), combining the extracts. Concentrate to a small volume (about 5 mL), using a rotary evaporator (*Test solution*). Apply separately, as 10-mm bands, 20 μL each of a solution containing about 0.5 mg of USP L-Methionine RS per mL (*Standard solution A*), a solution of USP Alliin RS in a mixture of methanol and water (1 : 1) containing 0.5 mg per mL (*Standard solution B*), and the *Test solution* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel, and allow the bands to dry. Develop the chromatograms in a mixture of butyl alcohol, *n*-propyl alcohol, glacial acetic acid, and water (3: 1 : 1 : 1) until the solvent front has moved about 8 cm from the origin. Remove the plate from the chromatographic chamber, and allow it to air-dry. Spray with a 0.2 in 100 solution of ninhydrin in a mixture of butyl alcohol and 2 N acetic acid (95 : 5), heat at 100° to 105° for about 10 minutes, and immediately examine the plate. The chromatogram of the *Test solution* shows many orange and pinkish violet zones: a violet zone having an R_f value of about 0.89, a pink zone having an R_f value (about 0.5) corresponding to that of the pink zone obtained from the chromatogram of *Standard solution A*, a pinkish zone having an R_f value of about 0.43, a strong orange zone having an R_f value of about 0.38, a pinkish violet zone having an R_f value (about 0.3) corresponding to that of the pinkish violet zone obtained from the chromatogram of *Standard solution B*, and additional pinkish orange zones situated very close to each other just below the zone attributed to alliin in the chromatogram of *Standard solution B*.

B: Transfer about 10 g of garlic bulbs that have been cut into small pieces to a suitable flask. Add 10 mL of 1 N sodium hydroxide and 10 mL of water, heat the flask in boiling water for 10 minutes, cool, and filter. Add a few drops of freshly prepared sodium nitroferricyanide TS to 2 mL of the filtrate: appearance of a red or orange-red color indicates the presence of sulfur-containing compounds in the test specimen.

C: The retention time of the major peak in the chromatogram of the *Test solution* corresponds to that in the chromatogram of the *Standard solution*, as obtained in the test for *Content of alliin*.

Total ash ⟨561⟩: not more than 5.0%.

Acid-insoluble ash ⟨561⟩: not more than 1.0%.

Water content ⟨561⟩: not more than 65.0% for fresh bulbs, and not more than 7.0% for dried bulbs.

Pesticide residues ⟨561⟩: meets the requirements.

Content of alliin—

0.045 M Phosphate buffer—Dissolve 1.24 g of monobasic sodium phosphate in 100 mL of water, adjust with 0.2 M sodium hydroxide to a pH of 7.1, dilute with water to 200.0 mL, and mix.

0.05 M Phosphate buffer—Dissolve 1.38 g of monobasic sodium phosphate in 100 mL of water, adjust with 0.2 M sodium hydroxide to a pH of 9.5, dilute with water to 200.0 mL, and mix.

0.01 M Carboxymethoxylamine hemihydrochloride solution—Dissolve 109 mg of carboxymethoxylamine hemihydrochloride in 100.0 mL of water.

Derivatization reagent—Dissolve 140 mg of *o*-phthaldialdehyde in 5 mL of methanol in a 50-mL volumetric flask, add 100 μL of *t*-butylthiol, dilute with *0.05 M Phosphate buffer* to volume, and mix. [NOTE—This reagent may occasionally become opaque during preparation. Store at room temperature, and use within one week.]

Mobile phase—Prepare a mixture of *0.045 M Phosphate buffer*, acetonitrile, 1,4-dioxane, and tetrahydrofuran (69.9 : 25.0 : 2.9 : 2.2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Alliin RS in a mixture of methanol and water (1 : 1), and dilute quantitatively, and stepwise if necessary, with a mixture of methanol and water (1 : 1) to obtain a solution having a known concentration of 0.05 mg per mL. Using a syringe, transfer 0.1 mL of this solution to a septum-capped vial, add 0.5 mL of the *Derivatization reagent*, and mix. Allow a reaction time of not less than 2 minutes before injection into the chromatograph.

Test solution—Transfer about 10.0 g of freshly peeled garlic cloves, accurately weighed, to a 110-mL homogenizing cup. Add 70.0 mL of *0.01 M Carboxymethoxylamine hemihydrochloride solution*, and blend at the highest speed for 30 seconds. Centrifuge, and decant the supernatant liquid into a 100-mL volumetric flask. Mix the remaining solids in the cup with 20 mL of *0.01 M Carboxymethoxylamine hemihydrochloride solution*, centrifuge, and add the supernatant liquid to the volumetric flask. Dilute the contents of the flask with *0.01 M Carboxymethoxylamine hemihydrochloride solution* to volume, and mix. Transfer 10.0 mL of the supernatant homogenate to a 100-mL volumetric flask, dilute with a mixture of methanol and water (1 : 1) to volume, and mix. Using a syringe, transfer 0.1 mL of this solution to a septum-capped vial, add 0.5 mL of the *Derivatization reagent*, and mix. Allow a reaction time of not less than 2 minutes before injection into the chromatograph.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 337-nm detector and a 4-mm × 10-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. [NOTE—Alliin exhibits two major peaks representing its diastereomers.] Chromatograph replicate injections of the *Standard solution*, and record the peak areas as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0% for each of the major peaks.

Procedure—Separately inject equal volumes (about 10 μL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the responses of the alliin diastereomer peaks. Calculate the percentage of alliin in the portion of Garlic taken by the formula:

$$100(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Alliin RS in the *Standard solution; W* is the weight, in g, of garlic cloves taken for the *Test solution;* and r_U and r_S are the sums of the peak responses for alliin diastereomers obtained from the *Test solution* and the *Standard solution*, respectively: not less than 0.5%, calculated on the dried basis, is found.

National Formulary 19

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National Formulary 19